3/10/75 DRAFT

Memorandum to Paul Berg from Joshua Lederberg

Subject: For Transmission to NIH Advisory Committee on Biohazards of DNA Experimentation.

Dear Paul,

This is in response to your solicitation of formal comments for the deliberation by the Biohazards Advisory Committee.

You may recall that I transmitted a number of writings to you during the course of the conference and if these are not already available as part of your committee's input, I would be grateful if you could return them to me for further rumination on points on which I may have been more alert at that time.

I do not envy the task that your committee faces, with its complex interdigitation of very difficult political and technical uncertainties. But I would earnestly caution you against overusing the apparently simple route of excessive "caution that can be mitigated later on," as I have heard expressed by a number of people. This may seem like a simple solution that can only be in the public interest, but I fear that exactly the opposite might happen. It is no more in the public interest to overbalance risks against benefits, than it would be to proceed carelessly, or to be oblivious of the possibility that hazards may be uncovered that have not been thought of in advance. But even more important than the direct social cost of delay in vital biomedical research is the problem of implementation and enforcement that absolutely depends on the credibility of the regulations.

In the mood that was expressed by some quarters at the conference, it might seem appropriate to seek out every conceivable hazard, no matter how remote, and incorporate that consideration into restrictive regulation. Even with the most cautiously laid-out guidelines, there are bound to be many marginal situations that are either of dubious importance, or where

there may be valid controversy about their application. The finer the net of a regulatory system, the more certain it is that these marginal situations will multiply and give rise to bitter recriminations about which research has been permitted and which has been restricted. Particularly in the circumstance that many innovative investigators will not have ready access to the facilities available for the prosecution of research labeled as "high risk", and that such facilities are more likely to be available to the renowned and accomplished investigators who are most likely to be consulted for advisory purposes, one can easily see the roots of a bitter polarization within the scientific community. The extent of this conflict will of course be accentuated by the degree to which a wide range of investigation is proscribed, and to the degree to which there are then significant differentials in the allowability of further research.

One might argue that even this was not too high a price to pay for the protection of public safety; but one must point out the ultimate limits to the enforceability of regulations of this kind - an enforcement that is certain to be the most effective as against the most responsible investigators and completely ineffectual against others. There really is no "crime" that can be specified, and it would be even more difficult to establish it after the fact - unlike the regulations about the handling of radioactive substances that are sometimes quoted as a parallel. Indeed since the hazards in question are so nearly hypothetical, objective verification of a transgression after the fact is even more difficult than it would be with respect to the rules for handling known pathogenic microorganisms. The quest for perfect enforcement can then be at best futile and at worst absolutely counterproductive, and it is for that reason that I myself would have placed far greater emphasis on mutual education than on any formal regulatory

scheme. Once one embarks upon the latter, one almost inevitably has a progressive escalation of bureaucratic frenzy to make the regulation work as it becomes apparent that it may not be succeeding! I do not have Hans Stetten's actual statement for more careful examination, but the remarks he was quoted about in the press would seem to bear out that this trend is already under way!

For these reasons my initial gloom was replaced by substantial optimism when I perceived the enthusiasm with which approaches based upon the development of disabled vectors was being pursued at the conference. This is, of course, a route that is free from many of the divisive difficulties of the obligatory use of physical containment facilities.

I would therefore urge your committee to give the most prompt and earnest attention to the promulgation of means for the continuation of the broad reach of more basically oriented research relying upon these vectors as the principal source of security. But the quest for absolute security against every conceivable hazard is bound to be a fatal one - and I would ask that you examine what the implications of such a policy would be if it were applied to any other aspect of microbiology, or even crop development, the handling of patients in hospitals, and even the analogy that we already discussed of international travel.

On balance it then seemed to me that the report of the plasmid committee, assuming that the adoption of the Mark-1 disabled vectors would allow some further relaxation of the restrictions, was right on target - and it was for that reason that I was dismayed and disappointed that the very carefully drawn distinctions that that committee had presented were not incorporated into the draft report of the conference as submitted by the organizing committee. The key element is what may have seemed like a very small technicality, the merger of categories 3 and 4 of the plasmid committee report under the general heading of "moderate risk". But an examination of the practical

implications of aggregating class 3 experiments into the moderate risk - containing requirements will show the grave implications of that seemingly simple lumping of the categories. I do not believe that the conference which had debated these points in great detail, and the report on which had been thrashed out after weeks of work, can be regarded in any sense as having voted affirmatively for the change in standards which might be implied by such an aggregation if that were to be stated as definitive policy. I believe the conference did rely upon the implied assurances by members of the organizing committee that this was not the intention in drafting the report of the conference and that all of this technical detail would be considered very carefully, very seriously and very sympathetically in the drafting of final regulations.

There are still significant problems of wording even in the plasmid report and the final report was drafted much too hastily to be useful as the basis of explicit policy. There are frequent references to the introduction of antibiotic-resistance into "species that do not already have it" and it should not take long to point out that we do not have a rigorous definition of microbial "species" that enable this expression to have a precise denotation. Of course, what was intended was the principle of "do no harm"! That is, do not create antibiotic resistant forms that either directly or by the further transmission of a drug-resistance plasmid will aggravate the problems of antibiotic therapy in its actual application to significant pathogens. But this is a slightly different concept from the one that is expressed in the document and it of course must take account of the actualities of which antibiotics are available for which infectious diseases, as well as some imponderables about the actual extent of genetic exchange among these strains in nature.

To use the case that I asked to be considered in detail at the conference, and which I think might be instructive at the present time, I find it difficult to understand any model under which the introduction of psc101 into Bacillus subtilis can be used as posing a therapeutic or ecological hazard by virtue of the tetracycline resistance which was the point at issue. (Let me hasten that for other reasons, as outlined in my memo to Dave Hogness, I am not seeking a special exemption here and would happily follow the path of pursuing experiments of this kind only with disabled vectors and hosts!) With some difficulty I can construct scenarios in which the introduction of any foreign plasmid into a prevalent ecotype like Bacillus subtilis might have some deleterious consequence, but this would be quite independent of whether or not tetracycline resistance was known to be involved in the initial transfer. And if one adopts the stance that no plasmids shall be exchanged as between species that "do not already do so," I think that there would be universal condemnation that this was far too restrictive a policy.

I have the impression that there was far too an intense a fixation on the problem of R factors and antibiotic resistance and it is interesting to note that almost all of the people who are professionally preoccupied with chemotherapy were in agreement. This issue should not be a surrogate for the broader and vaguer one of unpredictable ecological alterations. Precisely because there does not appear to be any credible boundary line that would permit any experimentation in microbiology at all, I would again favor the approach of the promulgation of disabled vectors and hosts as the routine basis of experimentation in this field without attempting the impossible task delineated in the previous paragraph.

To continue briefly with the issue of antibiotic resistance, one must keep in mind that the development of new antibiotics is likely to be impeded by severe restrictions on research bearing on the genetics of microorganisms,

which must include antibiotic-producing forms, research which is certain to be considerably enhanced by the new tools of DNA recombination if permitted to proceed.

My summary recommendation would come very close to simply urging the adoption of the principles of the plasmid committee report as presented to the conference, with concrete reference to the utilization of disabled vectors and hosts as a means of reducing the restrictions that have to be imposed on experiments of patently marginal risks.

As far as oncovirus experimentation is concerned, I believe that there are some central questions that can be readily pursued in high containment laboratories that would help to clarify the essential problems at issue. For this reason I would not criticize the section of the draft conference report that dealt with these problems as an interim approach pending more concrete information on the questions like transforming capability of DNA segments that have been amplified (in experiments in a high containment laboratory.) Even these, I would agree, should proceed only with the benefit of the safest biological systems that can be foreseen in the proximate future.

With respect to eukaryotic DNA, I believe it was a fallacy to grade the potential for risk on the basis of simple phylogenetic concepts. The arthropods uniquely share the role of important viral vectors with man and for the other reasons also outlined in my memorandum to David Hogness, they may present remarkably high risk potentials compared to others. Where there is any likelihood of the importation of wild viruses, I would of course adhere to the same standards as applied to viral experiments. However, people who are interested in pursuing research on the human genome should have recourse to sources like the WI-38 cell strain (which has been certified to be free from such viruses - and indeed had better be on account of its very wide applicability for the production of vaccines!) Such a strain of cells may well be a far safer source of important and interesting genetic informational DNA than, let us say, domestic cat or even cold-

blooded or invertebrate material that has not yet been extensively investigated for the possibility of carriage of such viruses.

Here again one can make effective use of the biocontainment approach to minimize the speculative hazards of the inadvertent production of toxigenic strains of E. coli.

My suggestions are therefore in close accord with the general recommendation of the report of the committee on eukaryote DNA with the suggestion that some areas of reduced hazard can be carved out of the arena of experiments involving human DNA, that there should be greater relative sensitivity to hazards from invertebrate material, and that all of these can be effectively mitigated - except where latent viruses are manifestly possible - by the simple application of biocontainment and the adoption of what amounts to a class 3 safety category.

To give a final recapitulation, I would certainly not be able to argue that these tempered measures will assure absolute safety from all risks; but I believe that

(1) they are the most likely to achieve the maximum protection that is de facto available in any practical system of regulation, and

(2) that the residual risks from this approach are:

    (a) far less than the potential benefits and

    (b) less than pertain to most other arenas of man's interaction with the microbial world, in the laboratory and out of it.

cc: Don Brown
Stan Falkow
Hans Stetten